REMARKS

Applicants' attorney wishes to thank the Examiner for the careful consideration given to this case. Claims 32-59 and 75-87 are pending in this application. Claims 32, 34, 35, 40, 55, 75, 78, 82, 86 and 87 have been amended for clarification and to correct typographical errors. No new matter has been added. Each of the rejections set forth in the Office Action are addressed below in the order presented therein.

35 U.S.C. § 112, second paragraph

Claims 32-59 and 75-87 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. In particular, the Examiner contends that the term "ICAM-1" may have more than one meaning and is thus not clear. Applicant has amended claims 32, 34, 35, 40, 75, 86 and 87 by the addition of the term "intracellular adhesion molecule-1" to clarify "ICAM-1" within the claims. Accordingly, this rejection should be withdrawn..

Claims 78 and 82 stand additionally rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The Examiner asserts that the term "the direct administration" lacks antecedent basis. Applicant has amended claims 78 and 82 to remove any antecedent basis issues, thereby rendering the Examiner's rejection moot.

35 U.S.C. § 103

Claims 32-59 and 75-87 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,096,722 to Bennett et al. (hereinafter, "the '722 patent") in view of Hammond et al., Nature Reviews Genetics 2001, Vol. 2:110-119 (hereinafter, "Hammond") and Vickers et al., Journal of Biological Chemistry, 2003, Vol 278:7108-7118 (hereinafter, "Vickers"). The Examiner alleges that the '722 Patent describes a method for modulating human ICAM expression by administration of antisense RNA "such that human ICAM is degraded," Hammond teaches that RNA interference is superior to antisense, and Vickers teaches that siRNA and RNase H-dependent antisense are both valid strategies for evaluating the function of genes in a cell-based assay. The Examiner contends that it would have been obvious to combine the teachings of the '722 Patent, Hammond and Vickers to arrive at Applicant's claimed invention. Applicant respectfully disagrees.

Effective Amount

Applicant respectfully assert that neither the '722 Patent nor Hammond or Vickers teach or suggest an effective amount of siRNA. Specifically, the '722 Patent describes a single stranded DNA antisense oligonucleotide and is necessarily silent as to an effective amount of siRNA. Furthermore, a person of ordinary skill would not be able to determine an effective amount.

Hammond merely suggests that siRNA may be utilized in humans *in the future* as is clearly indicated by the designation of "Human ?" in the column labeled "RNAi in the future" in Table 2 and provides no indication that siRNA is effective in humans at all. Therefore, Hammond can provide absolutely no indication of *how* effective siRNA is in a human in general, much less how effective siRNA targeting ICAM-1 mRNA is in a human. Accordingly, Hammond is necessarily silent as to an "effective amount" of siRNA to degrade ICAM-1 mRNA in a human. Furthermore, the citations identified by the Examiner are completely irrelevant with regard to the effectiveness of siRNA in humans based on the teachings of Hammond *as a whole* (*see* MPEP 2141.02). Specifically, the "diverse organisms" referred to by Hammond would include *C. elegans*, *Drosophila*, Plants, *Planaria*, and *Trypanisome* (*see* Table 2). Clearly, these "diverse organisms" are far removed from a human, and the effectiveness of siRNA in these organisms has little bearing on the applicability of siRNA in humans. Similarly, Hammond's statement that "RNAi is a potent method, requiring only a few molecules..." is clearly directed to the efficacy of siRNA in *C. elegans* as evidenced by the context of this phrase:

> "In *Caenorhbditis elegans*, gene silencing by RNAi can be initiated simply by soaking worms in dsRNA or by feeding *worms* Escherichia coli that express dsRNA. RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression. Not only can silencing spread from the digestive tract of *worms* to the remainder of the organism..." (pg. 110, col. 1, emphasis added).

Applicant asserts that an effective amount of siRNA in *C. elegans* would necessarily be different than an effective amount of siRNA in humans. Moreover, the skilled artisan could only guess the total amount of siRNA delivered to an organism that is soaked in siRNA or fed bacteria that continually produce siRNA. Therefore, Hammond fails to cure the deficiencies of the '722 Patent.

Vickers purportedly shows that both siRNA and RNase H dependent degradation of gene silencing are "valid approaches." However, Vickers specifically describes a number of factors that cause a difference in activity between siRNA and RNase H including: target site, different mechanism of action (*i.e.*, siRNA degrades mRNA in cytoplasm and RNase H degrades pre-mRNA in the nucleus) and secondary structure of pre-mRNA (pg. 7116, col. 2). Moreover, Vickers cites variability in the art with regard to the efficacy of siRNA (pg. 7116, col. 2 to pg. 7117, col. 1) and Vickers specifically states that "[i]t remains to be determined whether siRNA molecules work broadly for *in vivo* applications" (pg. 7117, spanning col. 1 and 2). Clearly, Vickers fails to teach or fairly suggest an effective amount of siRNA to degrade ICAM-1 mRNA in a human, and Vickers fails to cure the deficiencies of the '722 Patent and Hammond.

Unpredictability

Even assuming *arguendo* the skilled artisan could combine the teachings of the '722 Patent, Hammond and Vickers, based on Hammond preparing an siRNA that effectively targets and degrades *any* human mRNA would yield unpredictable results and, therefore, successfully using siRNA to inhibit ICAM-1 expression would require undue experimentation. Specifically, Hammond states that knocking out your favorite gene in "plants, flies, mice or cultured cells" "*might one day* become reality" since "[h]ow this phenomenon works is *slowly* becoming clear, and might help us develop an effortless tool to probe gene function in cells and animals" (*see* Abstract, emphasis added). Hammond appears to believe that useful siRNA for probing even cultured cells is technology that may be available in the future, but is certainly not feasible at the time of writing. Moreover, Hammond specifically points out that siRNA is not uniformly effective (Table 2: "Works, but some limitations") and identifies a number of mutants that for which siRNA is ineffective (Table 1).

Based on Hammond as whole, in combination with the other cited references, the skilled artisan would have no expectation that human ICAM-1 could be targeted by siRNA, and a method such as that provided in the pending claims would not yield predictable results. In fact, the Examiner has suggested that the use of siRNA to inhibit expression of ICAM-1 would result in unpredictable results in the enablement rejections presented in the Office Actions of August 25, 2006 and May 15, 2007. In withdrawing this rejection, the Examiner concedes that the subject matter of the pending claims is only enabled by Applicant's own work thereby providing additional evidence that the combination of the '722 Patent, Hammond and Vickers is not

obvious. Therefore, any obviousness rejection levied by the Examiner requires impermissible hindsight bias based on the Examiner's own admission.

Applicant fails to see the relevance of Vickers in the outstanding rejection. Based on the Examiner's comments, it would appear that the Examiner believes Vickers provides a means by which the antisense molecules of the '722 Patent degrade target mRNA citing Vickers' reference to RNase H-mediated degradation and claiming that "RNase mediated degradation would be coincident with siRNA designed to bind the same position on the target mRNA..." (Office Action pg. 6, 1st full paragraph). Applicants respectfully submit that RNase H recognizes RNA-DNA heteroduplexes (see Vickers, pg. 7108, col. 2, 2nd full paragraph) and not RNA-RNA duplexes. Thus, RNase H would not degrade RNA-RNA duplexes as would form upon binding of siRNA to the target mRNA, and any disclosure pertaining to RNase H would have no bearing on either siRNA technology or Applicant's pending claims which are clearly directed to RNA: "siRNA comprising a sense RNA strand and an antisense RNA strand, wherein the sense and the antisense RNA strands form an RNA duplex." Moreover, RNase H is confined to the nucleus and would not be available in the cytoplasm to degrade siRNA mediated mRNA-siRNA duplexes. Therefore, Vickers fails to cure the deficiencies of either the '722 Patent or Hammond.

The '722 Patent is Non-analogous Art

Finally, the '722 Patent is not analogous art with regard to either the pending claims or the other cited references because the '722 Patent fails to disclose or even suggest a molecule having a similar structure and function to siRNA of the pending claims (*see* MPEP 2141.01(a) II).

Structure: Applicant clearly claims a molecule having a structure that includes double stranded RNA having a sense strand and an antisense strand. The '722 Patent only describes an antisense strand and provides absolutely no suggestion or motivation to prepare either a sense strand or a double stranded RNA molecule. Furthermore, the antisense molecules of the '722 Patent must be chemically modified. The '722 Patent clearly states that "modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as, for example, ..." (col. 9, lns 20-24) and describes numerous examples of such chemical modifications (col. 9, ln. 24 – col. 13, ln. 64). Based on this discussion, the skilled artisan at the time of invention would expect an unmodified antisense RNA molecule to be degraded when

introduced into a living human cell necessitating the modification of the antisense molecules of the '722 Patent. Therefore, neither strand of Applicant's recited double-stranded RNA fits within the defined structure of the antisense molecule of the '722 Patent.

Function: Contrary to the Examiner's assertion, the '722 Patent does NOT teach that "the human ICAM-1 mRNA is degraded," and nowhere in any of the passages cited by the Examiner (*i.e.*, Abstract, Summary of the Invention and claims 7, 9 and 11) is the degradation of ICAM-1 mRNA even suggested. Rather, the '722 Patent teaches: "Hybridization of antisense oligonucleotides with mRNA interferes with one or more of the normal functions of mRNA" and describes antisense oligonucleotides as interfering translocation of RNA, protein translation, splicing and catalytic activity of mRNA (col. 7, lns 56-65). Therefore, the antisense molecules of the '722 Patent do not have the same function as Applicant's claimed double stranded RNA.

Moreover, even assuming *arguendo* the antisense oligonucleotides of the '722 Patent degrade mRNA by an RNase H mechanism as described in Vickers, RNase H mediated degradation as described by Vickers is directed to pre-mRNA and not mRNA, the target of siRNA and occurs in a different compartment of the cell because pre-mRNA is confined to the nuclease and mRNA is in the cytoplasm (pg. 7116, col. 2 *et seq.*). Accordingly, Vickers provides additional evidence that the antisense oligonucleotides of the '722 Patent have a different function than siRNA.

Based on the foregoing, the antisense molecules of the '722 Patent do not have the same structure or the same function as the siRNA recited in the pending claims. Thus, the '722 Patent cannot be considered analogous prior art (MPEP 2141), and the Examiner's rejection should be withdrawn for at least this reason.

CONCLUSION

Applicant asserts that the pending claims are in condition for final allowance and respectfully requests notification to such effect. Should the Examiner have any questions or comments, or need any additional information from Applicants' attorney, she is invited to contact the undersigned at her convenience.

In the event that an additional fee is required for this Response, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0436.

Respectfully submitted,

By: _____
Raymond A. Miller
Reg. 42,891

Dated: April 11, 2008
PEPPER HAMILTON LLP
500 Grant Street
One Mellon Bank Center, 50th Floor
Pittsburgh, PA 15219
(412) 454-5813
(412) 281-0717 - facsimile

Attorney Ref.: 129402.00701

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.10

In re Application of:	:	Express Mail No.: ER195154311US
REICH et al.	:	Confirmation No.: 1285
Application No.: 10/759,878	:	Group Art Unit No.: 1635
Filed: January 16, 2004	:	Examiner: Terra C. Gibbs

For: COMPOSITIONS AND METHODS FOR SIRNA INHIBITION OF ICAM-1

I HEREBY CERTIFY THAT THE DOCUMENTS DESCRIBED BELOW ARE BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE VIA EXPRESS MAIL UNDER 37 CFR 1.10 ON **APRIL 11, 2008** AND ARE ADDRESSED TO: MAIL STOP AMENDMENT, COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450.

Emily E. Scattaregia
(Typed/printed name of person mailing paper or fee)

Emily E. Scattaregia
(Signature of person mailing paper or fee)

Documents Enclosed:

Documents Sent:
☒ Postcard;
☒ Certificate of Mailing;
☒ Response to Non-final Office Action;
☒ Petition for Extension of Time Under 37 CFR 1.136(a);
☒ Credit Card Payment Form.